REMARKS

In the Office Action mailed March 26, 2007, claims 11-24, 38-49 and 56-81 were withdrawn from consideration. The Continuity Data was requested to be amended. Claims 25-32 and 50-55 were rejected under 35 U.S.C. 112, first paragraph. Claims 1-10, 25-32, 50-55 and 82-83 were rejected under 35 U.S.C. 112, second paragraph.

Continuity Data

In the Office Action mailed March 26, 2007, the Examiner expressed confusion in the Continuity Data section. Applicants thank the Examiner for pointing out this issue, and has adopted the suggestion helpfully given for the wording of the Continuity Data section. No new matter is added by the amendment of this section of the application.

35 U.S.C. 112, first paragraph

In the Office Action mailed March 26, 2007, claims 25-32 and 50-55 were rejected under 35 U.S.C. 112, first paragraph. The Office Action stated:

> Applicants do not disclose in the instant application, as can best be determined, the claimed methods wherein the high affinity TCR exhibits a dissociation constant for the ligand greater than about 10^7 or about 10^7 to about 10^{10}. . . The instant application and the prior art do not provide any guidance as to how the protein structure of TCRs can be manipulated so as to generate TCRs with the recited dissociation constants for any given ligand. While applicants can assay the dissociation constants for high affinity TCRs – ligand combinations, such assays do not satisfy the written description requirement of 35 USC 112, 1st paragraph because applicants have not provided a disclosure sufficient for the skilled artisan to envision a representative number of species sufficient to describe the claimed genus. Applicants do not provide a structure-function relationship between the structures of the high affinity TCRs and their function of having dissociation constants in the recited ranges for any given ligand. The skilled artisan would therefore conclude

> that applicants were not in possession of the claimed invention.

In response, applicants have provided a disclosure sufficient for the skilled artisan to envision a representative number of species sufficient to described the claimed genus. Applicants provide extensive description of the techniques to carry out the claimed invention without undue experimentation (for example, page 30, lines 9-12; and examples on page 30 through page 34, for example).

The Office Action states "While applicants can assay the dissociation constants for high affinity TCRs – ligand combinations, such assays do not satisfy the written description requirement of 35 USC 112, 1st paragraph because applicants have not provided a disclosure sufficient for the skilled artisan to envision a representative number of species sufficient to describe the claimed genus."

In response, it is believed a skilled artisan can, in fact, envision a representative number of species which describe the claimed genus. The state of the art of binding affinity assays is well developed. In Fig. 3 and the detailed description provided in the specification, the applicants show a binding affinity assay in which soluble TCRs are used at varying concentrations to measure the binding affinity of the interaction with its cognate peptide/MHC (QL9/Ld). This exact assay had been used routinely by the applicants and others prior to the current filing (see Schlueter, C. J., Manning, T. C., Schodin, B. A., and Kranz, D. M. (1996) "A residue in the center of peptide QL9 affects binding to both Ld and the T cell receptor," J. Immunol. *157*, 4478-4485; and Manning, T. C., Schlueter, C. J., Brodnicki, T. C., Parke, E. A., Speir, J. A., Garcia, K. C., Teyton, L., Wilson, I. A., and Kranz, D. M. (1998) "Alanine scanning mutagenesis of an alpha beta T cell receptor: mapping the energy of antigen recognition," Immunity *8*, 413-425).

In addition, other assays to measure the affinities of TCR:pepMHC interactions had already been established at that time, as described in detail in a 1998 review by Davis et al (see pages 524 – 528 of Davis, M. M., Boniface, J. J., Reich, Z., Lyons, D., Hampl,

J., Arden, B., and Chien, Y. (1998) "Ligand recognition by alpha beta T cell receptors," Annu Rev Immunol *16*, 523-544). These assays included the technique of surface plasmon resonance which yielded binding affinities measurements that were very similar to those obtained by the assay method used by the applicants (see pg 525, Davis et al, 1998). In their review, Davis and colleagues show the binding affinity measurements for over a dozen TCR:pepMHC interactions (Tables 1 and 2). While the affinities of the TCRs measured prior to this application were for wild type TCRs, it is well known in the fields of biochemistry and immunology that proteins (e.g. TCRs) with affinities in the higher affinity range of 10^7 M^{-1} to 10^{10} M^{-1} would be even easier to measure by the standard techniques known in the art. This fact stems most directly from two properties of higher affinity interactions: the need for less soluble protein when affinities are higher, and the reduced non-specific interactions that occur at these lower protein concentrations. These factors are well known in the art.

The additional explanation provided above and the references discussed (these references were cited by applicant on an Information Disclosure Statement filed July 20, 2004) provide evidence that the inventors had possession of the claimed invention and that a skilled artisan could envision a representative number of species sufficient to describe the claimed genus. In view of the above arguments and amendments, it is believed that all rejections under 35 U.S.C. 112, first paragraph are overcome. Reconsideration and withdrawal of the rejections is respectfully requested.

<u>35 U.S.C. 112, second paragraph</u>

In the Office Action mailed March 26, 2007, claims 1-10, 25-32, 50-55 and 82-83 were rejected under 35 U.S.C. 112, second paragraph.

The Office Action stated: "Claims 1, 25 and 33 (and dependent claims) are vague in that it is unclear what ligands applicants are attempting to identify. Applicants claim use of high affinity TCRs to 'identify ligands'. . . Since the high affinity TCRs are designed to bind to their cognate ligand at higher affinities than the wild-type TCR, it is unclear if the

high affinity TCRs are used here to identify their cognate ligand or any (undefined) ligand."

In response, claims 1, 25 and 33 have been amended to clarify the ligands are peptide/MHC ligands. The amendment to claim 1 is supported by claim 3, which has been cancelled as duplicative. The amendment to claim 25 is supported by claim 27, which has been cancelled as duplicative. The amendment to claim 33 is supported by claim 35, which has been cancelled as duplicative.

Claims 4 and 6 were said to be vague "in that applicants recite '[l]abeling said high affinity TCRs with a label that binds to the selected peptide/MHC ligand." In response, Applicants have clarified claims 4 and 6.

Claim 7 was said to be vague "in the recitation of the phrase '[c]ontacting said high affinity TCR with cells.' Two different high affinity TCRs are recited in the claim, a high affinity TCR and a labeled high affinity TCR." In response, Applicants have clarified the claim.

Claim 10 was said to be vague "in that applicants recite a label that binds to specific peptide/NHC ligands." In response, claim 10 has been clarified.

Claims 25-26 and 50-55 were said to be vague "because applicants recite dissociation constants . . . but do not recite any units of measurement with these numbers." In response, claims 25-26 and 50-55 have been clarified to recite the units M^{-1}, which is an art-recognized standard unit of dissociation constant.

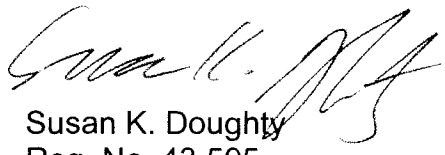
No new matter has been added by any amendment, and all amendments are supported by the specification and claims as filed.

In view of the above arguments and amendments, it is believed that all rejections under 35 U.S.C. 112, second paragraph are overcome. Reconsideration and withdrawal of the rejections is respectfully requested.

CONCLUSION

This response is accompanied by a Petition for Extension of Time (three months) and an authorization to charge the fee due (believed to be $1020.00 for a three month extension of time) to Deposit Account No. 07-1969. If this is incorrect however, please charge any fees required, including any extensions of time required, to Deposit Account No.07-1969.

Respectfully submitted,



Susan K. Doughty
Reg. No. 43,595

GREENLEE, WINNER AND SULLIVAN, P.C.
4875 Pearl East Circle, Suite 200
Boulder, CO 80301
Telephone: (303) 499-8080
Facsimile: (303) 499-8089
E-mail: usptomail@greenwin.com
Attorney Docket No. 89-99A